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L1: Entry 1 of 3

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Jun 12, 2001

DOCUMENT-IDENTIFIER: US 6245530 B1

TITLE: Receptor ligand

DEPR:

The expression pattern of the VEGFR-3 (Kaipainen et al., Proc. Natl. Acad. Sci. USA, 92:3566-70 (1995)) suggests that VEGF-C may function in the formation of the venous and lymphatic vascular systems during embryogenesis. Constitutive expression of VEGF-C in adult tissues shown herein further suggests that this gene product also is involved in the maintenance of the differentiated functions of the lymphatic endothelium where VEGFR-3 is expressed (Kaipainen et al., 1995). Lymphatic capillaries do not have well formed basal laminae and an interesting possibility remains that the silk-like BR3P motif is involved in producing a supramolecular structure which could regulate the availability of VEGF-C in tissues. However, as shown here, VEGF-C also activates VEGFR-2, which is abundant in proliferating endothelial cells of vascular sprouts and branching vessels of embryonic tissues, but decreased in adult tissues. Millauer et al., Nature, 367:576-78 (1993). These data have suggested that VEGFR-2 is a major regulator of vasculogenesis and angiogenesis. VEGF-C may thus have a unique effect in lymphatic endothelium and a more redundant function shared with VEGF in angiogenesis and possibly permeability regulation of several types of endothelia. Because VEGF-C stimulates VEGFR-2 and promotes endothelial migration, a utility for VEGF-C is suggested as an inducer of angiogenesis of blood and lymphatic vessels in wound healing, tissue transplantation, in eye diseases, in the formation of collateral vessels around arterial stenoses and into injured tissues after infarction.

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L1: Entry 2 of 3

File: USPT

Oct 10, 2000

DOCUMENT-IDENTIFIER: US 6130071 A

TITLE: Vascular endothelial growth factor C (VEGF-C)
.DELTA.Cys.sub.156 protein and gene, and uses thereof

DEPR:

The expression pattern of the VEGFR-3 (Kaipainen et al., Proc. Natl. Acad. Sci. (USA), 92:3566-70 (1995)) suggests that VEGF-C may function in the formation of the venous and lymphatic vascular systems during embryogenesis. Constitutive expression of VEGF-C in adult tissues shown herein further suggests that this gene product also is involved in the maintenance of the differentiated functions of the lymphatic and certain venous endothelia where VEGFR-3 is expressed (Kaipainen et al., 1995). Lymphatic capillaries do not have well-formed basal laminae and an interesting possibility exists that the silk-like BR3P motif is involved in producing a supramolecular structure which could regulate the availability of VEGF-C in tissues. However, as shown here, VEGF-C also activates VEGFR-2, which is abundant in proliferating endothelial cells of vascular sprouts and branching vessels of embryonic tissues, but not so abundant in adult tissues. Millauer et al., Nature, 367:576-78 (1993). These data have suggested that VEGFR-2 is a major regulator of vasculogenesis and angiogenesis. VEGF-C may thus have a unique effect on lymphatic endothelium and a more redundant function, shared with VEGF, in angiogenesis and possibly in regulating the permeability of several types of endothelia. Because VEGF-C stimulates VEGFR-2 and promotes endothelial migration, VEGF-C may be useful as an inducer of angiogenesis of blood and lymphatic vessels in wound healing, in tissue transplantation, in eye diseases, and in the formation of collateral vessels around arterial stenoses and into injured tissues after infarction.

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USPT	(VEGF adj C or VEGF-C) near5 angiogen\$	3	<u>L1</u>

The EMBO Journal Vol 15, pp.290-298, 1996, Copyright © European Molecular Biology Organization

A novel vascular endothelial growth factor, VEGF-C, is a ligand for the Flt4 (VEGFR-3) and KDR (VEGFR-2) receptor tyrosine kinases [published erratum appears in EMBO J 1996 Apr 1;15(7):1751]

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Angiogenesis, the sprouting of new blood vessels from pre-existing ones, and the permeability of blood vessels are regulated by vascular endothelial growth factor (VEGF) via its two known receptors Flt1 (VEGFR-1) and KDR/Flk-1 (VEGFR-2). The Flt4 receptor tyrosine kinase is related to the VEGF receptors, but does not bind VEGF and its expression becomes restricted mainly to lymphatic endothelia during development. In this study, we have purified the Flt4 ligand, VEGF-C, and cloned its cDNA from human prostatic carcinoma cells. While VEGF-C is homologous to other members of the VEGF/platelet derived growth factor (PDGF) family, its C-terminal half contains extra cysteine-rich motifs characteristic of a protein component of silk produced by the larval salivary glands of the midge, *Chironomus tentans*. VEGF-C is proteolytically processed, binds Flt4, which we rename as VEGFR-3 and induces tyrosine autophosphorylation of VEGFR-3 and VEGFR-2. In addition, VEGF-C stimulated the migration of bovine capillary endothelial cells in collagen gel. VEGF-C is thus a novel regulator of endothelia, and its effects may extend beyond the lymphatic system, where Flt4 is expressed.

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